CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022519Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Donna Griebel, MD
Subject	Division Director Summary Review
NDA#	022519
Applicant Name	Horizon Therapeutics, Inc.
Date of Submission	March 23, 2010
PDUFA Goal Date	April 23, 2011
Proprietary Name / Established (USAN) Name	Duexis ibuprofen and famotidine
Dosage Forms / Strength	Tablet (Ibuprofen 800 mg/famotidine 26.6 mg)
Proposed Indication(s)	For the reduction of the risk of development of ibuprofen-associated, upper gastrointestinal ulcers in patients who require use of ibuprofen
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Ali Niak, MD/ Lynne Yao, MD
Biostatistical Review	Wen Jen Chen, PhD/Mike Welch, PhD
Pharmacology Toxicology Review	Dinesh Gautam, PhD/Sushanta Chakder, PhD
CMC Review	Gene Holbert, PhD/Y. Tang, PhD/ Moo Jhong Rhee, PhD
Clinical Pharmacology Review	P.F.Bai, PhD/Sue-Chih Lee, PhD
Biopharmaceutics Review	H. Mahayni, PhD/Patrick Marroum, PhD
DDMAC	R. Szydlo/K Jones
DSI	K. Malek, MD, PhD/T. Purohit-Sheth, MD G. Biswas, PhD/M. Yau, PhD
CDTL Review	Lynne Yao, MD
OSE/DMEPA	Y. Maslov/Zachary Oleszczuk, Pharm D
DRISK	L. Ford, RN, BSN, MBA/S Griffiths, RN, MSHS-PH, BSN/B Fuller, RN, MSN, CWOCN
OSE	P. Greene
PMHS	A. Karesh, MD/ H.C. Sachs, MD/L. Mathis, MD
SEALD	J. Delasko, RN, MS/A. Trentacosti, MD

OND Office of New Drugs
DDMAC Division of Drug Marketing, Advertising and Communication
OSE Office of Surveillance and Epidemiology
DMEPA Division of Medication Error Prevention and Analysis
DRISK
DSI Division of Scientific Investigations
CDTL Cross Discipline Team Leader
PMHS Pediatric and Maternal Health Staff
SEALD Study Endpoints and Labeling

Division Director Review

1. Introduction

This NDA, submitted under 505(b)(2) section of the Federal Food, Drug and Cosmetic Act and 21 CFR Part 314.50, seeks approval of a fixed combination of ibuprofen 800 mg and famotidine 26.6 mg. The product is a (b) (4) combination, intended to be dosed three times a day. (b) (4) The reference products for this application were: Pepcid tablets for the famotidine component and IBU for the ibuprofen component. The innovator ibuprofen product is Motrin.

Famotidine's indications include short-term treatment of active duodenal ulcers (40 mg once a day at bedtime or 20 mg BID); maintenance therapy for duodenal ulcers (20 mg once a day at bedtime); short-term treatment of active benign gastric ulcers (40 mg once a day); short-term treatment of gastroesophageal reflux disease (20 mg twice a day for up to 6 weeks; 20 or 40 mg twice daily up to 12 weeks for erosive esophagitis); and treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison Syndrome, and multiple endocrine adenomas, for which the label states "doses up to 160 mg every 6 hours have been administered to some adult patients with severe Zollinger-Ellison syndrome").

Ibuprofen's indications include relief of the signs and symptoms of rheumatoid arthritis and osteoarthritis; relief of mild to moderate pain, and treatment of primary dysmenorrhea. The approved doses of ibuprofen differ, depending on the specific indication. For the arthritis indications the recommended daily dose is 400 mg, 600 mg, or 800 mg three or four times a day. The IBU label's Dosage and Administration section states that "individual patients may show a better response to 3200 mg daily, as compared with 2400mg, although in well-controlled clinical trials patients on 3200 mg did not show a better mean response in terms of efficacy. Therefore, when treating patients with 3200 mg/day, the physician should observe sufficient increased clinical benefits to offset potential increased risk. The dose should be tailored to each patient, and may be lowered or raised depending on the severity of symptoms either at time of initiating drug therapy or as the patient responds or fails to respond. In general patients with rheumatoid arthritis seem to require higher doses of IBU tablets than do patients with osteoarthritis. The smallest dose of IBU tablets that yields acceptable control should be employed. A linear blood level dose-response relationship exists with single doses up to 800 mg. The availability of three tablet strengths facilitates dosage adjustment. In chronic conditions, a therapeutic response to therapy with IBU tablets is sometimes seen in a few days to a week but most often is observed by two weeks. After a satisfactory response has been achieved, the patient's dose should be reviewed and adjusted as required." The label states that the dose for the other two indications is lower, i.e., 400 mg every 4-6 hours for mild to moderate pain, and 400 mg every 4 hours as needed for dysmenorrhea.

The applicant's proposed indication was (b) (4)

This proposed indication does not adequately address the indication for the ibuprofen

component of this fixed combination product. The proposed dosing schedule for Duexis is one tablet three times a day dosing. In light of the 800 mg ibuprofen content in Duexis, the indication for the ibuprofen component must be limited to the rheumatoid arthritis and osteoarthritis indications.

To support this 505(b)(2) application, the Applicant conducted pharmacokinetic studies of each component of Duexis to establish a bridge with the referenced NDAs. These studies are described in the Clinical Pharmacology section of this review. In addition, the applicant investigated the efficacy and safety of Duexis for reduction of upper gastrointestinal (UGI) ulcers associated with the ibuprofen component in two phase 3 trials of 6 months duration, in which the Duexis was compared to ibuprofen 800 mg, dosed three times daily.

This review will focus on the major review issues identified in this application, which included: 1) a conclusion by the Clinical and Statistical reviewers that one of the two phase 3 trials did not provide persuasive evidence of effectiveness, while the second trial did provide highly persuasive evidence of efficacy, 2) examination of the potential for nephrotoxicity, 3) manufacturing inspectional issues, 4) inspection issues identified by DSI at both the clinical sites for the phase 3 trials and a key bioequivalence study, and 5) labeling issues related to appropriately describing the observed efficacy and the limitations of the clinical trials to support the efficacy of Duexis in patients at higher risk of NSAID- induced UGI ulcers, due to patient age or history of prior UGI ulcer. I will address how each of these issues were evaluated and resolved to support an approval recommendation.

2. Background

Ibuprofen, a nonsteroidal anti-inflammatory drug (NSAID), was first approved in 1974. Its indications and associated doses were presented in Section 1 above. The toxicities of NSAIDs are well characterized and include gastrointestinal (GI) tract injury. The NSAIDs carry a boxed warning that includes a warning about "serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal….Elderly patients are at greater risk for serious gastrointestinal events." The Warnings section of the ibuprofen label provides more detailed information on gastrointestinal effects and states that "Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue with longer duration of use…..NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or gastrointestinal bleeding. Patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding who use NSAIDs have a greater than 10-fold increase risk for developing a GI bleed….Other factors that increase the risk of GI bleeding in patients treated with NSAIDS include…older age…Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore, special care should be taken in treating this population…."

Famotidine, an H_2-receptor antagonist (H_2-RA), was first approved in 1981. As discussed in Section 1 above, it does not carry an indication of risk reduction of ulcers caused by NSAIDs. Products that have been approved for that indication include misoprostol and the proton pump inhibitors lansoprazole and esomeprazole. The development plans for these products targeted

patients at high risk for development of ulcers during exposure to NSAIDs, specifically based on history of ulcers and/or age. The relevant label content is summarized below:

1) **Lansoprazole's** indication for Risk Reduction of NSAID-Associated Gastric Ulcer states: "indicated for reducing the risk of NSAID-associated gastric ulcers in patients with a history of a documented gastric ulcer who require the use of an NSAID. Controlled studies did not extend beyond 12 weeks. Patients ranged in age from 23 to 89 years (median age 60 years), with 65% female patients.."

2) The **esomeprazole** indication states "indicated for the reduction in the occurrence of gastric ulcers associated with continuous NSAID therapy in patients at risk for developing gastric ulcers. Patients are considered to be at risk due to their age (≥ 60) and/or documented history of gastric ulcers. Controlled studies do not extend beyond 6 months." Patients ranged in age from 19 to 89 (median age 66.0 years) with 70.7% female… At baseline, the patients in these studies were endoscopically confirmed not to have ulcers but were determined to be at risk for ulcer occurrence due to their age (≥60 years) and/or history of a documented gastric or duodenal ulcer within the past 5 years.

3) **Misoprostol** label states it is indicated " in patients at high risk of complications from gastric ulcer, e.g., the elderly and patients with concomitant debilitating disease, as well as patients at high risk of developing gastric ulceration, such as patients with a history of ulcer." As summarized in Table 24 of the CDTL review, in one trial the mean age was 74 years and 18% of participants had a history of ulcer. In another trial the mean age was 60 years and 7% of participants had a history of ulcer.

The labeling for Vimovo, an NSAID combination product that contains esomeprazole, does not mention the degree of risk of patients. The clinical trial description in the label, however, states that patients who entered the clinical trials had to have a documented history of gastric or duodenal ulcer with the past 5 years if they were less than age 50 years. The label states the majority of patients in the trial (83%) were in the age range of 50-69 years (and 67% were female). The Clinical review for Vimovo indicates the mean age was 60 years. The reference product, Nexium, already carried the risk reduction indication (as described above).

All of the labels focus on reduction of risk of gastric ulcer, and only the Nexium label mentions duodenal ulcers. That label states that a statistically significant reduction in duodenal ulcers was not observed "due to low incidence." Although the Vimovo label does not mention duodenal ulcers, the FDA Statistical review of that NDA notes that duodenal ulcers were a prespecified important secondary endpoint and that the Vimovo applicant reported the analysis of this secondary endpoint showed a statistically significant treatment effect of Vimovo compared to naproxen.

The applicant for the current NDA for Duexis proposed a broader "NSAID gastroprotection" indication (upper gastrointestinal, including both gastric and duodenal ulcers) than what the previously approved products have (reduction of risk of gastric ulcer). The FDA reviewers

had concerns about allowing the broader indication and concerns about the strength of the submitted evidence to support the customary (narrower) gastric ulcer reduction indication. The biostatistical and clinical reviews of this NDA did not agree with the applicant's primary efficacy analyses, including utilization of life table analyses and the exclusion of patients who dropped out of the study early. Relevant to this review issue was the existence of a Special Protocol Assessment (SPA) for each of the two phase 3 trials submitted in support of this application. SPA agreement was documented on **December 19, 2006**. The agreement included two features critical to the final analyses: 1) how study dropouts would be handled and 2) the statistical analysis methods to be used. The final SPA agreement for Study 301 stated that only patients with a documented and protocol defined gastric or duodenal ulcer would be counted as a treatment failure. Drop-outs for any other reasons, including adverse events, would not be considered treatment failures (i.e., considered to have developed an ulcer). The final SPA agreement also specified that the primary analysis would be the Cochran-Mantel-Haenszel (CMH) test of proportions as the primary analysis method.

The applicant submitted a request to increase the sample size (s) of the phase 3 clinical trials on May 22, 2007. The Agency replied on **August 31, 2007** that changes in sample size would constitute a change in the SPA and nullify the SPA agreement. In response, the applicant chose to limit changing the sample size to only one of the two phase 3 trials (Study 303). Therefore, the SPA agreement was nullified for study 303 but remained in force for study 301. Subsequently, in **October 30, 2008**, after reviewing the statistical analysis plan(s) for the trials, which was submitted (September 2008) after the SPA agreement was reached, the Agency recommended both life table analysis and crude rate analysis be performed, and that both "should show positive results….in both randomized and treated populations." This recommendation was prompted by the fact that the submitted statistical analysis plan indicated that the Kaplan-Meier method would be used to estimate proportions. In the pre-NDA meeting on December 17, 2009, the Agency stated that the crude rate analysis, with early terminators considered treatment failures, would be the analysis presented in product labeling. The Agency did suggest that it would be open to considering the exclusion of the early terminators from the worst case analysis those patients whom the applicant could provide documentation that the termination was not related to treatment (or treatment failure). Ultimately, during labeling negotiations for this NDA, the applicant reverted to use of the originally specified CMH test.

3. CMC/Biopharmaceutics

I concur with the conclusions reached by the chemistry reviewers that the NDA has provided sufficient CMC information to assure the identity, strength, purity and quality of the drug product. An "acceptable" recommendation was received from the Office of Compliance on March 31, 2011.

The famotidine drug substance is manufactured (b) (4)
The ibuprofen drug substance is manufactured (b) (4) The drug product, stability testing, bulk packaging and quality control testing is performed at Pharmaceutics, International Inc. (Pii). It performs packaging, labeling, quality control and batch release of drug product.

A Form 483 was issued at the prior approval inspection of Pii. The deficiencies prompted an Official Action Indicated (OAI) for the Pii facility and the Office of Compliance recommended a withhold approval action. The deficiencies were subsequently addressed by the facility in a response to the Form 483, and the OC DMPQ changed its recommendation to approval.

The to-be-marketed product differs from the product utilized in the phase 3 trials. The CMC reviewer describes the differences in detail in his review, and the Clinical Pharmacology reviewer describes the pharmacokinetic studies that were conducted to establish the that phase 3 trial data could be used to support the product that will be marketed. The CMC reviewer noted that the phase 3 product stability lots showed increases in famotidine impurities, and these data prompted the applicant to investigate new formulations. The differences in the products are summarized in the table below, which is reproduced from the CMC review.

Table 1.

Comparison of the Composition of the HZT-501 (b) (4) Stability Prototype Formulation to the HZT-501 Commercial Formulation

Component (Prototype)	Amount in Tablet (mg)	Component (Commercial)	Amount in Tablet (mg)
(b) (4)			

(b

(b) (4)

[redacted]

Biopharmaceutics

The Biopharmaceutics reviewer identified no approvability issues. The following dissolution method and specifications were found to be acceptable, based on the reviewer's discussions with the applicant during the course of the review (modifications of the specifications proposed at the time of submission of the NDA, based on the FDA review findings):

Dissolution Apparatus:	USP <711> Apparatus II (Paddle)
Dissolution Medium:	50 mM Potassium Phosphate Buffer, pH 7.2
Dissolution Medium Volume:	900 mL
Temperature in Vessel:	37.0º C ± 0.5° C
Speed:	50 rpm
HZT-501 Tablet Dissolution Specification:	Q = (b) (4) at 15 minutes for ibuprofen
	Q = (b) (4) at 30 minutes for famotidine

4. Nonclinical Pharmacology/Toxicology

This is a 505(b)(2) application. Both ibuprofen and famotidine have been marketed for decades. The ibuprofen dose in this application does not exceed the previously approved dose and the total daily dose of famotidine in this application does not exceed the total daily doses mentioned in the famotidine label. Bridging is described in the Clinical Pharmacology section of this review, but the Pharmacology/Toxicology team leader stated that the fact that the total daily dose of famotidine in Duexis is lower than doses found in the Dosage and Administration section of the Pepcid tablet label creates an adequate bridge between Duexis and Pepcid tablet for nonclinical data. Based on the pharmacokinetic studies submitted in this application, the Clinical Pharmacology reviewers also concluded that the famotidine 26.6 mg dose in Duexis, dosed three times a day, is not expected to exceed exposures in three of the doses currently found in the Pepcid label (including 40 mg once a day, 40 mg twice a day, and the 160 mg every 6 hour doses for hypersecretory conditions). The Applicant submitted pharmacology/toxicology studies from the published literature. The impurities observed in the

product were found to be within acceptable ranges defined by the ICH Q3B(R2) guidance. I concur with the FDA Pharmacology reviewers' conclusions that there are no outstanding pharmacology/toxicology issues that preclude approval. I concur with their labeling recommendations.

5. Clinical Pharmacology

The Clinical Pharmacology reviewers identified no outstanding clinical pharmacology issues that preclude approval. Their labeling recommendations were incorporated in label negotiations. The Clinical Pharmacology reviewers recommended the Applicant should be required to conduct pediatric pharmacokinetic studies as part of their pediatric development plan.

The sponsor conducted a series of single dose bioequivalence studies to support this 505(b)(2) application. These studies primarily focused on demonstrating bioequivalence of the ibuprofen in the applicant's products to the reference ibuprofen product, IBU. The Clinical Pharmacology reviewer noted that the applicant submitted phase 3 clinical trials to establish the safety and efficacy of the famotidine component of Duexis (for the new proposed famotidine indication), which is a lower dose than some of the approved Pepcid doses. For the famotidine component of Duexis, the 505(b)(2) information derived from the Pepcid tablet label to support approval/labeling of Duexis included nonclinical information, information on special populations, and well-described famotidine safety issues. The scientific bridge between the famotidine 26.6 mg component of Duexis and Pepcid is primarily needed to understand the relative pharmacokinetics between Duexis and Pepcid, in order to gain assurance that the nonclinical data that supported the Pepcid approval can in fact support Duexis, and that there are no large exposure differences predicted by the pharmacokinetics of the products that would cause the reviewers to conclude that safety labeling in the Pepcid label are not applicable to the Duexis label. The Pharmacology/toxicology reviewer noted that because the total daily dose of Duexis is less than labeled dosing regimens of Pepcid, the nonclinical data from Pepcid can be used to support the Duexis NDA. Clinical and Clinical Pharmacology reviewers concluded that reference to the Pepcid tablet was adequate based on comparisons of famotidine exposure associated with each product. That analysis follows below.

The comparison of the pharmacokinetics of the famotidine component of the proposed product (26.6 mg) to the referenced product (Pepcid 40 mg) was covered in an addendum review by the Clinical Pharmacology reviewers. They state in their review that to provide assurance, from a safety standpoint for the bridge between the two products, the data from two studies conducted by the applicant and included in the NDA submission were explored and compared. In one, Study HZ-CA-001, the pharmacokinetics of the referenced product (Pepcid 40 mg) were described within the context of a single-dose drug interaction study (with Motrin 800 mg). These pharmacokinetic data were compared to the pharmacokinetic data for the famotidine component of the proposed product (26.6 mg) obtained from a second study, Study HZ-CA-016, a single-dose food effect study that evaluated the to-be-marketed formulation of Duexis. The Clinical Pharmacologist predicted steady-state famotidine exposure (Cmax and AUC) based on a famotidine 26.6 three times a day (tid) dose that was estimated using the PK

data from the single dose food effect study. Using this estimate of the steady-state exposure for the famotidine component of Duexis, a comparison with the referenced product could be performed. This comparison revealed that the exposure following famotidine, 26.6 mg, tid, was lower than that following a single dose of Pepcid, 40 mg. These data are summarized in the table below, which is reproduced from her addendum review.

Table 2. Comparison of famotidine Cmax and AUC values following multiple dose Duexis dosed three times a day (estimated) and single dose Pepcid 40 mg

	Pepcid single dose (famotidine 40 mg)	Duexis tid Famotidine 26.6 mg
Cmax	136 ng/ml	95.92 ng/ml
AUC0-infinity	866 ng-h/ml	613.8 ng-h/ml

The CDTL and I concluded that this information established the necessary bridge to the Pepcid tablet NDA referenced by the applicant. Although the Clinical Pharmacology reviewer stated that further support for the cross study comparison approach could be gleaned from an additional submitted study that utilized Pepcid suspension, those data were limited in value for this purpose because they were obtained in patients with renal impairment and Pepcid is eliminated largely through the kidney (65-70%). Furthermore, the PK profile of Pepcid would expected to change based on the patient's glomerular filtration rate, but this change is not necessarily predictable because Pepcid appears to be cleared through the kidney by both glomerular filtration and tubular secretion. Based on this comparison, it was apparent that the daily exposure to famotidine in Duexis (26.6 mg tid) would be predicted to fall below that associated with the approved Pepcid dosing regimens: 40 mg per day, 40 mg BID for 12 weeks to treat erosive esophagitis, and "doses up to 160 mg every 6 hours."

The pharmacokinetics of the ibuprofen and famotidine components of Duexis were further characterized, as described below. It should be noted that the final to-be-marketed formulation, referred to in reviews as HZT-501, is not the formulation studied in the phase 3 trials, and the ibuprofen tablets (referred to as HZT-405) selected for administration in the control arm of the phase 3 trials were not the reference product, IBU. (For this reason a bioequivalence trial was necessary to establish that the comparator in the phase 3 trials is bioequivalent to the reference product, IBU). The goals of key bioequivalence studies are listed below:

1) Demonstration of the bioequivalence of the phase 3 control arm ibuprofen product, HZT-405, to the reference drug, IBU (demonstration of bioequivalence of the ibuprofen in each formulation). [HZT-405 vs. IBU]

2) Demonstration of the bioequivalence of ibuprofen as part of the HZT-501 product administered in the phase 3 trials to the reference drug, IBU (demonstration of bioequivalence of the ibuprofen in each formulation). [phase 3 HZT-501 ibuprofen vs. IBU]

3) Demonstration of the bioequivalence of ibuprofen as part of the to-be-marketed HZT-501 product to the reference drug, IBU (demonstration of bioequivalence of the ibuprofen in each formulation). [to be marketed HZT-501 ibuprofen vs. IBU]

4) Demonstration of bioequivalence of ibuprofen as part the phase 3 HZT-501 product to ibuprofen as part of the to-be-marketed HZT-501 [phase 3 HZT-501 ibuprofen vs. to-be-marketed HZT-501 ibuprofen]

5) Demonstration of the bioequivalence of the famotidine component of the phase 3 HZT-501 product to the famotidine component of the to-be-marketed HZT-501. [phase 3 HZT-501 famotidine vs. to be marketed HZT-501 famotidine]

The Clinical Pharmacology reviewers determined that each of these goals were achieved, with the exception of demonstrating bioequivalence of ibuprofen as a component of the phase 3 product to the ibuprofen as a component of the to-be-marketed product. For that comparison, the lower bound of the 90% confidence interval of the ratio of the commercial product to the phase 3 formulation was just below 80% (at 77.8%) for Cmax. AUC in that comparison fell within the confidence interval range generally applied for assessing bioequivalence. The reviewers determined that this did not impact approvability of the product for the ibuprofen component of the commercial product because the commercial product did meet bioequivalence criteria in the comparison to the reference product IBU. These data are summarized in the table below, which is reproduced from the Clinical Pharmacology review.

Table 3 Pharmacokinetic Parameters and Ratios for Ibuprofen in the HZT-501 Phase 3 product, the reference product (IBU) and the HZT-501 to-be-marketed product. (Ratios defined at bottom of table)

	HZT-501 Phase 3 Formulation Mean (SD)	Ibuprofen 800 mg Mean (± SD)	HZT-501 (b) (4) Formulation Mean (± SD)	Ratio C / A[1] (90% CI) %	Ratio A / B[1] (90% CI) %	Ratio C / B[1] (90% CI) %
n	35	35	34			
T_{max} (h)	1.47 (± 0.705)	1.89 (± 1.05)	1.91 (± 0.616)	--	--	--
C_{max} (µg/mL)	55.0 (± 9.30)	49.6 (± 10.4)	44.9 (± 7.55)	81.5 (77.8, 85.3)	111.5 (106.5, 116.8)	90.9 (86.8, 95.2)
$AUC_{0\text{-}last}$ (µg-h/mL)	195 (± 37.9)	196 (± 38.9)	202 (± 39.5)	100.3 (97.2, 103.4)	99.7 (96.7, 102.8)	102.5 (99.4, 105.7)
$AUC_{0\text{-}inf}$ (µg-h/mL)	196 (± 38.0)	198 (± 38.7)	204 (± 39.6)	102.8 (99.7, 106.0)	99.7 (96.7, 102.8)	102.5 (99.4, 105.7)
$t_{½}$ (h)	2.21 (± 0.360)	2.16 (± 0.454)	2.23 (± 0.412)	--	--	--

A = single-dose HZT-501 Phase 3 formulation; B= IBU 800 mg; C= single-dose HZT-501 to-be-marketed product

Reanalysis of the data excluding a single subject, based on the recommendation of the DSI review from the DSI inspections of the clinical and analytical proportions of the bioequivalence study (HZ-CA-0-15), did not change the observed outcome.

I concur with the reviewers' conclusions regarding the ibuprofen component of the commercial HZT-501. As part of this 505(b)(2) application, it is necessary for the ibuprofen component of the proposed product to be bioequivalent to the reference product. I am not concerned by the somewhat low ibuprofen Cmax ratio of the commercial to the phase 3 HZT-501. It does not negatively impact interpretation of the phase 3 clinical trial data, since the goal of that study was to establish the efficacy of the famotidine component of the combination product. If the commercial product ibuprofen to phase 3 product ratio had been high, that could have caused concerns about whether the gastroprotective efficacy observed in the phase 3 trials could be used to support the efficacy of the famotidine in the commercial product.

I also concur with the Clinical Pharmacology reviewers that the bioequivalence evaluation of famotidine between the phase 3 product and the to-be-marketed product established bioequivalence of the two products, even with the exclusion of a single subject, as recommended by the DSI review. As discussed in detail above, there was no direct bioequivalence evaluation of the 26.6 mg famotidine dose of the phase 3 or to-be-marketed HZT-501 famotidine component compared to a 26.6 mg dose of the reference product Pepcid, with the exception of a renal impairment study in 5 patients with moderate or severe renal insufficiency (creatinine clearances ranged from 20.41 ml/min to 40.43 ml/min in these 5 patients). In that study the pharmacokinetic evaluations included a comparison of the famotidine as part of HZT-501 to a suspension containing 26.6 mg of Pepcid. The ratios for Cmax and AUC, along with the 90% confidence intervals are summarized in the table below, which is reproduced from the Clinical Pharmacology review.

Table 4: Ratios of the Pharmacokinetics Parameters for Ibuprofen and Famotidine Following Oral Administration of HZT-501 and Following Concurrent Oral Administration of Equivalent Doses of Commercially Available Ibuprofen and Famotidine

Parameter	Ibuprofen			Famotidine		
	Ratio[1]	Lower Limit	Upper Limit	Ratio[2]	Lower Limit	Upper Limit
C_{max}[3]	86.9	60.0	125.8	115.8	83.1	161.4
AUC[4]	85.5	65.1	112.1	103.9	78.4	137.9

[1] HZT-501 / ibuprofen 800 mg; 2 HZT-501 / famotidine 26.6 mg; 3 µg/mL for ibuprofen;

The upper limit of the ratio for Cmax exceeds 125%, but not the AUC. As described above, these data are of limited value to establish a bridge for the famotidine in Duexis to Pepcid suspension because all five patients had significant renal impairment.

Additional Clinical Pharmacology review observations that factored into the FDA's labeling discussions included their findings from the food effect study. The Clinical Pharmacology reviewer noted that the food effect study did not indicate that fasting or postprandial (high fat meal) pharmacokinetics significantly changed for the two drugs between the two states. (Ibuprofen stayed within the 80-125% bioequivalence acceptance range. For famotidine, the lower bound of the confidence interval of fed/fasted ratio fell slightly below the lower limit, to 77.9%.) However, the product labeling will not state that the product can be taken on an

empty stomach. The current ibuprofen label states in the Dosage and Administration section that "If gastrointestinal complaints occur, administer MOTRIN tablets with meals or milk." Patients are frequently instructed to take NSAIDs with food to improve gastrointestinal tolerability. In addition, the clinical trials supporting the Duexis application did not specify whether patients should take the product with or without food, and we have to assume that patients in the trials took the product both with and without food. We cannot determine based on study conduct or the clinical data collected in the trials whether there is enhanced tolerability with Duexis taken without food compared to ibuprofen alone.

The summary data from the drug interaction study that included an evaluation of the impact of a famotidine 40 mg dose on ibuprofen pharmacokinetics are summarized below in a table reproduced from the Clinical Pharmacology review.

Table 5: Pharmacokinetics Parameters (mean ± SD) for Ibuprofen and Famotidine 40 mg When Administered Alone and In Combination (N = 6)

Parameter	Ibuprofen		Famotidine	
	Alone	With Famotidine	Alone	With Ibuprofen
t_{max} (hr)	2.25 ± 1.89	1.58 ± 0.49	2.08 ± 1.02	1.75 ± 0.42
C_{max} (*)	51.9 ± 7.8	60.0 ± 10.9	136 ± 36.6	166 ± 41.0
AUC (**)	244 ± 63.5	242 ± 69.1	866 ± 234	1006 ± 215
$t_{1/2}$ (hr)	2.49 ± 0.54	2.33 ± 0.74	3.73 ± 0.35	3.92 ± 0.35

* ng/mL for famotidine; µg/mL for ibuprofen
** ng-h/mL for famotidine; µg-h/mL for ibuprofen

The reviewers concluded that these data demonstrated that coadministration increased the AUC and Cmax of famotidine by 16% and 22%, respectively. The Cmax of ibuprofen increased somewhat as well, by approximately 15.6%. The interaction data based on the single 40 mg dose of famotidine had relevance because the 40 mg dose exposure would be expected to cover (worse case, since it actually exceeds) the famotidine exposure anticipated with 26.6 mg famotidine dosed three times daily. The Clinical Pharmacology reviewers pointed out that in light of the high standard deviations, the changes observed are not statistically significant, and they concluded that there is no significant interaction between ibuprofen and famotidine. The reviewers again noted that the 40 mg famotidine dose evaluated in this study exceeds the 26.6 mg famotidine dose in Duexis, and pointed to a comparison of the estimated famotidine steady state pharmacokinetics predicted for Duexis to that observed for a single dose of Pepcid. This comparison, presented earlier in this review, supports that there is a lower famotidine steady state exposure with Duexis than associated with a single dose of Pepcid 40 mg. They also examined the individual patient data for the 6 patients and found that the increase in ibuprofen Cmax was driven by 2 patients, one of whom had an aberrant curve that suggested other factors (perhaps altered gastrointestinal motility) was involved in the differences in data collected. Based on this information, I concluded that the increase in Cmax of ibuprofen observed in this trial should not raise a safety concern that impacts approvability of Duexis.

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In summary, I concur that the pharmacokinetic data are adequate to support use of the phase 3 data submitted in this application and the applicant's designated reference products to support approval of this 505(b)(2) application for Duexis.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

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Two phase 3 trials (Study 301 and 303) were submitted to support the efficacy of the famotidine component of Duexis for the new proposed indication, and at the new dose, administered three times daily. Both were multicenter, randomized (2:1), double-blind, parallel-dose trials of 6 month duration that compared Duexis dosed three times daily to ibuprofen 800 mg three times daily. The primary endpoint of Study 301 was proportion of patients who developed at least one endoscopically-diagnosed upper gastrointestinal (i.e., gastric and/or duodenal) ulcer (of unequivocal depth and at least 3 mm in diameter) over the 6 month period. Endoscopies were to be performed at weeks 8, 16 and 24. The primary endpoint of Study 303 was proportion of patients who developed at least one endoscopically diagnosed gastric ulcer. Upper gastrointestinal ulcer was a secondary endpoint in 303. Gastric ulcer was a secondary endpoint in 301. Duodenal ulcer was a secondary endpoint in both trials.

Patients were eligible if they were between 40 and 80 years of age, and had not used NSAIDs within the 30 days prior to study entry and who were expected to require daily administration of an NSAID for at least the coming 6 months. Patients with a history of upper gastrointestinal ulcer were excluded if they had a history of ulcer complications including perforation, gastric outlet obstruction, and gastrointestinal bleeding. Randomization was stratified based on the concomitant use of low-dose aspirin and/or other anticoagulant medication or history of upper gastrointestinal ulcer. Patients with H. pylori infection were also excluded, unless they had "adequate treatment and provision of a current negative test result." Ultimately, the median age in each trial was: Study 301 54.0 (mean 55.4) Study 303 55.0 (mean 55.7) [in the primary analysis population defined by the applicant]. Additionally, 82% of the patients enrolled overall for both studies were less than 65 years of age. Only 6 % of the combined trial populations had a history of upper gastrointestinal ulcer. Advanced age and history of upper gastrointestinal ulcer are important risk factors for developing upper gastrointestinal ulcers in patients who are taking an NSAID. The products previously approved for the risk reduction of NSAID-associated gastric ulcers are listed in the table below (reproduced from the CDTL review). Many of the clinical trials that supported previous approvals enrolled patients at high risk relative to the population enrolled in the Duexis phase 3 trials.

Table 6: Summary of previous risk reduction of NSAID-associated gastric ulcer trials

	Incidence of GUs	Risk Difference[2]	Relative Risk (95% CI)[3]	Risk Factors	NSAIDs Used
Misoprostol ± NSAIDs					
Misoprostol Endoscopy Study 1 (12 weeks) – EGD at Weeks 0, 4, 8, and 12					
Misoprostol 200 µg QID (n=74)	1 %	24%	0.1 (<0.1, 0.4)	Mean age = 74 years old Hx of ulcer = 18%	ibuprofen, piroxicam, naproxen
Placebo (n=76)	25%				
Misoprostol Endoscopy Study 2 (12 weeks) – EGD at Weeks 0, 4, 8, and 12					
Misoprostol 200 µg QID (n=65)	3%	15%	0.2 (<0.1, 0.8)	Mean age = 60 years old Hx of ulcer = 7%	ibuprofen, piroxicam, naproxen
Placebo (n=62)	18%				
PPIs ± NSAIDs					
Lansoprazole Study (12 weeks) – EGD at Weeks 0, 4, 8, and 12					
Lansoprazole 15 mg/day (n=136)	20%	29%	0.4 (0.3, 0.6)	Mean age 60 years Hx of GU = 99% Hx of DU = 50% Low dose aspirin use = 19%	ibuprofen, piroxicam, naproxen, diclofenac
Placebo (n=133)	49%				
Esomeprazole Study 1 (26 weeks) – EGD at Weeks 0, 4, 12, and 26					
Esomeprazole 20 mg/day (n=191)	5%	7%	0.4 (0.2, 0.9)	Mean age = 64 Hx of PUB 26% Hx of POB = 1% Low dose aspirin use = 10%	COX-2 = 14% Non-selective = 85%
Placebo (n=184)	12%				
Esomeprazole Study 2 (26 weeks) – EGD at Weeks 0, 4, 12, and 26					
Esomeprazole 20 mg/day (n=267)	5%	12%	0.3 (0.1, 0.5)	Mean age = 66 Hx of PUB = 10% Hx of POB = 1% Low dose aspirin use = 12%	COX-2 = 39% Non-selective = 61%
Placebo (n=257)	17%				
Esomeprazole/Naproxen Study 1 (26 weeks) – EGD at Weeks 0, 4, 12, and 26					
Esomeprazole/naproxen (20/500 mg) BID (n=218)	4%	19%	0.2	Mean age = 60 Hx of PUB =5% Low dose aspirin use = 24%	Naproxen
Naproxen 500 mg BID (n=216)	23%				
Esomeprazole/Naproxen Study 2 (26 weeks) – EGD at Weeks 0, 4, 12, and 26					
Esomeprazole/naproxen (20/500 mg) BID (n=210)	7%	17%	0.3	Mean age = 60 Hx of PUB = 11% Low dose aspirin use = 23%	Naproxen
Naproxen 500 mg BID (n=210)	24%				
Esomeprazole ± Low-Dose Aspirin (75 to 325 mg) – 26 week study[13] EGD at Weeks 0, 8, and 26					
Esomeprazole 20 mg (n=493)	1%	3%	0.3	Mean age = 69	Low dose aspirin
Placebo (n=498)	4%				

[1] The primary endpoint for some of these endoscopy trials was the proportion of patients without GUs during the treatment period. Although in other trials, the primary endpoint was the proportion of patients free from GUs, the data are presented as the proportion of patients without GUs for consistency.
[2] The risk difference was the difference between the incidence of GUs in the control group and the gastroprotective product group.

The protocols for Study 301 and 303 were submitted for review under Special Protocol Assessments, and the record indicates that agreement was reached in December 19, 2006. As noted in the CDTL review the applicant's prespecified analysis of the primary efficacy endpoint in Study 301, as agreed upon in the SPA, was "a crude rate analysis counting only patients who had a documented ulcer as a treatment failure using the Cochran-Mantel-Haenszel analysis" (CMH). The Statistical team leader states in his addendum review that the CMH method "is generally preferred, but because of drop-outs, results from both the CMH and Life Table meds depended on missing data patterns and assumptions." The applicant

submitted a request to increase the sample sizes of the clinical trials in May 2007, and reports that these changes were made based on re-evaluation of the literature, which changed the assumptions upon which the original power analysis had been based. The Agency informed the applicant that a change in sample size would constitute a change in the protocol and would nullify the SPA agreement. Based on that, the applicant increased the sample size of only one of the phase 3 trials, Study 303, in September 2007. Subsequently, in October 2008, upon review of the statistical analysis plan that was submitted in September 2008, the Agency noted that the applicant's primary analysis plan was a Kaplan Meier (KM) method. The Statistical team leader stated in his addendum review that this change would have constituted lack of compliance to the SPA. The FDA reviewers at the time of that review recommended that instead of a KM analysis, that a Life Table analysis was preferable to a KM analysis. At the December 2009 pre-NDA meeting the Agency informed the applicant that for product labeling purposes, the efficacy analysis of interest would be the crude rate analysis with patients who left the study early being considered treatment failures.

The Statistical and Clinical reviews of the Studies 301 and 303 carefully discussed and evaluated how to appropriately interpret the data generated in these two trials. The SPA agreement and the communication between the FDA and applicant were reviewed in order to understand which analyses were associated with valid agreements. Of particular interest were a determination of which patients should be included in the efficacy analyses (i.e., how to handle patients with missing efficacy data due to early termination), the appropriate primary endpoint (whether upper gastrointestinal ulcer, which includes duodenal ulcer, was an appropriate endpoint), and what the appropriate analysis methodology was (Kaplan-Meier/Life Table/CMH).

The applicant's primary efficacy analysis population, or "primary population," was defined as those patients who received at least one dose of study drug and who underwent a baseline endoscopic examination and at least the first scheduled endoscopic evaluation (8 weeks ± 2 weeks). The FDA clinical reviewers expressed concern that this analysis excluded patients who may have left the study due to symptoms caused by an underlying but undocumented ulcer (due to absent endoscopy) within the first 8 weeks. The Statistical team leader notes in his addendum review that the Agency's "usual preference for the primary analysis population has been the ITT based on all subjects randomized (or a modified ITT based on all randomized and treated) and it would be unlikely that an analysis population excluding subjects up to 8 weeks into the study would have been agreed to given current thinking." He discussed this further with the clinical team during label negotiations with the applicant, and noted that in Study 301, a similar proportion of subjects in each arm were excluded from the efficacy analysis based on the population definition that excluded patients who terminated without having the week 8 endoscopy. After that discussion, it was concluded that these exclusions, at worst, would have all been patients who had undiagnosed ulcers, and that there was no reason to expect a higher likelihood of developing an ulcer early in the study if treated with the combination product. Based on this, he concluded that from a statistical view the randomization "would likely be preserved." The concerns about the analysis population definitions had prompted the Clinical and Statistical reviewers to examine a series of exploratory analyses during the review cycle. These analyses included classification of early dropouts as ulcer events and are described in detail in the Statistical and CDTL reviews.

Ultimately, the reviewers explored the outcome data from Studies 301 and 303 utilizing multiple definitions for the analysis populations and multiple classifications of patients with missing data to explore the robustness of the observed efficacy outcomes. Crude rate analyses were the primary focus of the FDA for these additional analyses. Sensitivity analyses yielded little impact on the observed outcome of Study 303, which had undergone a revision of the sample size during the conduct of the trial. Study 301, however, demonstrated shifts in the p values with the various analysis approaches. The Statistical reviewer and Clinical reviewer concluded that Study 301 did not provide persuasive evidence of efficacy, but Study 303 was highly robust and could, therefore, stand alone as providing persuasive evidence of efficacy. The CDTL noted that the overall efficacy results also provided persuasive evidence of efficacy. The Statistical reviewers expressed some concern that the applicant (during the conduct of the trial) had changed the sample size of the only trial providing what the reviewers considered robust evidence of efficacy. However, this change occurred relatively early in a blinded trial and the reviewers could find no evidence that the change was made based on an interim look at the trial data. In light of the fact that the eligibility criteria for these trials defined a lower risk population than has been enrolled in previous "NSAID gastroprotection" trials, it is conceivable that additional data external to the trial could have come available to the applicant during its conduct to make them aware that it risked being underpowered, based on the population defined by eligibility criteria.

After evaluating the totality of evidence from Study 301 and 302, the CDTL and Statistical reviewer recommended approval of the product. The CDTL stated that "The data presented by the applicant in this submission provides substantial evidence to support the approval of the product." She noted that the results of Study 303 were highly statistically significant and persuasive. She acknowledged that when the prespecified primary analysis of the primary endpoint of Study 301 was evaluated, the applicant was able to demonstrate a statistically significant difference. The Statistical reviewer stated that "…based upon the efficacy data provided by Study 303, one may conclude that the effect of study drug HZT-501 is supported with persuasive evidence for the proposed indication of reduction of the risk of ibuprofen-associated upper gastrointestinal (i.e., gastric and/or duodenal)ulcers in patients who require use of ibuprofen."

The FDA reviewers recommended presentation of crude rate analyses (utilizing CMH) in the label and the applicant was amenable to this. In fact, the (b) (4) provided less favorable outcomes for Duexis relative to ibuprofen. However, the reviewers and the applicant disagreed on the following points for labeling efficacy:

1) The applicant disagreed that the protocol defined efficacy analysis population should be modified for labeling purposes. (The FDA did not support presentation of the efficacy population that excluded the patients who terminated from the study early without the 8 week endoscopy or subsequent endoscopy if an earlier endoscopy did not show an ulcer, and carrying the last observation forward for the last endoscopy for early terminators without endoscopy at the time of termination.) They argued that the analysis based on the protocol specified efficacy analysis population should be presented in

labeling because it had been subject to a Special Protocol Assessment agreement with FDA.

2) The applicant disagreed with limiting presentation of the efficacy data to the analysis of the gastric ulcer endpoint. (The FDA has not permitted labeling of duodenal ulcers or combined upper gastrointestinal ulcer NSAID product claims for other products.) The applicant argued that the protocol specified primary endpoint of Study 301 was upper gastrointestinal ulcers defined as gastric ulcer and/or duodenal ulcer. Study 301 was subject to a SPA agreement. They argued that the analysis of the combined gastric and/or duodenal ulcer endpoint in Study 303 was a prespecified secondary endpoint and was valid to conclude as statistically significant, in light of the highly statistically significant outcome of the analysis of the gastric ulcer primary endpoint. They pointed out that even though the number of duodenal ulcers in both trials was low, the analysis of the duodenal ulcer secondary endpoint yielded a statistically significant difference between treatment arms, using their analysis methodologies, in both trials.

3) The applicant did not agree with presenting the most conservative analyses that counted missing data as a treatment failure. They again pointed to the SPA agreement for Study 301. They stated that these "sensitivity" analyses can only be viewed as exploratory.

4) The applicant disagreed that the data from the subgroup efficacy analyses of patients 65 years and older and the patients with a history of gastric ulcer should be presented in labeling, particularly if presented in a fashion that stated that these data did not demonstrate that Duexis was effective in these subgroups.

Please see the CDTL review, Clinical review, Statistical review and Addendum to Statistical review for a comprehensive summary of the efficacy analyses that were evaluated in this application. Ultimately, during labeling negotiations, the FDA concurred with the applicant's proposal to include the upper gastrointestinal ulcer analysis in the Clinical Studies section of the label and the words "upper gastrointestinal ulcer, which in the clinical trials was defined as a gastric and/or duodenal ulcer" in the indication, because it was the primary efficacy analysis in the SPA agreement, and because the applicant's prespecified secondary endpoint analysis of the duodenal ulcer (component of this primary endpoint) was statistically significant. Although the CDTL noted concerns that the p-value for the duodenal ulcer shifted in sensitivity analyses in Study 301, utilizing the analysis population specified in the SPA, the difference was statistically significant, and was replicated in Study 303. The "combined" upper gastrointestinal ulcer data will be presented for each trial, and will be clearly identified as a secondary endpoint for Study 303. The gastric ulcer data will also be presented. The duodenal ulcer data will only be presented as it appears as a component of the "combined" upper gastrointestinal ulcer analyses. The CDTL and clinical team strongly opposed including the duodenal ulcer analyses in the product label because they did not consider these analyses to

be convincing evidence of the effect of HZT-501 in preventing duodenal ulcers. The CDTL pointed out in her review that "H. pylori testing was not performed in patients who developed duodenal ulcers, and it is possible that some of these patients developed H. pylori infection as the cause of the duodenal ulcers. Furthermore, the duodenal ulcer rates were low in both studies, making clear conclusions difficult to draw despite the statistically significant difference observed in study 303."

The FDA also agreed to allow presentation of the analyses based on the primary population, as defined by the applicant as the primary efficacy analysis population in both protocols, because it had been agreed to in the SPA. Two analyses for each endpoint in each study will be presented. The first analysis, the applicant's preferred analysis, will be the efficacy analysis in which patients who have at least one endoscopy post baseline who terminate early without a documented endoscopically-diagnosed ulcer are considered to be ulcer free at the time of termination from study. The second analysis will be one in which patients who have at least one endoscopy post baseline who terminate early are considered to have an ulcer if they leave the study because of adverse event, loss to follow-up, discretion of investigator, or did not have an endoscopy performed within 14 days of the last dose of study drug. Those data are summarized below. The label narrative will state that both analyses exclude patients who terminate study prior to the first scheduled endoscopy at 8 weeks. It should be noted that the data from Site 389 was removed from analyses of Study 303 based on the recommendation of DSI. (See Section 11 of this review for further explanation.) Removal of site 389 did not change the efficacy results substantively.

Table 7: Overall Incidence Rates of Patients Who Developed at Least One Upper Gastrointestinal or Gastric Ulcer - Study 301

	DUEXIS % (n/N)	**Ibuprofen % (n/N)**	***P*-value[a]**
Primary endpoint			
Upper gastrointestinal ulcer*	10.5% (40/380)	20.0% (38/190)	0.002
Upper gastrointestinal ulcer**	22.9% (87/380)	32.1% (61/190)	0.020
Secondary endpoint			
Gastric ulcer*	9.7% (37/380)	17.9% (34/190)	0.005
Gastric ulcer**	22.4%% (85/380)	30.0% (57/190)	.0.052

[a] Cochran-Mantel-Haenszel test

* Classifying early terminated patients as NOT having an ulcer

** Classifying patients who early terminated due to an adverse event, were lost to follow-up, discontinued due to the discretion of the sponsor or the investigator, or did not have an endoscopy performed within 14 days of their last dose of study drug, as having an ulcer

Table 8 Overall Incidence Rate of Patients Who Developed at Least One Gastric or Upper Gastrointestinal Ulcer - Study 303

	DUEXIS % (n/N)	Ibuprofen % (n/N)	*P*-value[a]
Primary endpoint			
Gastric ulcer*	8.7% (39/447)	17.6% (38/216)	0.0004
Gastric ulcer**	17.4% (78/447)	31.0% (67/216)	<0.0001
Secondary endpoint			
Upper gastrointestinal ulcer*	10.1% (45/447)	21.3% (46/216)	<0.0001
Upper gastrointestinal ulcer**	18.6% (83/447)	34.3% (74/216)	<0.0001

[a] Cochran-Mantel-Haenszel test

* Classifying early terminated patients as NOT having an ulcer

** Classifying patients who early terminated due to an adverse event, were lost to follow-up, discontinued due to the discretion of the sponsor or the investigator, or did not have an endoscopy performed within 14 days of their last dose of study drug, as having an ulcer

To address the concerns about the limited data and evidence that Duexis was effective in patients ≥65 years of age or in patients with a history of gastric ulcer, the proposed label was modified as follows:

1) The indication was modified to include information on the limitations of the data for Duexis to support that it will be effective in elderly patients and in patients with a history of upper gastrointestinal ulcers. Both groups are high risk patients and there is little evidence to support use of this product in those populations. The indication will state:

"DUEXIS, a combination of the NSAID ibuprofen and the histamine H_2-receptor antagonist famotidine, is indicated for the relief of signs and symptoms of rheumatoid arthritis and osteoarthritis and to decrease the risk of developing upper gastrointestinal ulcers, which in the clinical trials was defined as a gastric and/or duodenal ulcer, in patients who are taking ibuprofen for those indications. The clinical trials primarily enrolled patients less than 65 years of age without a prior history of gastrointestinal ulcer. Controlled trials do not extend beyond 6 months. [see Clinical Studies (14) and Use In Specific Populations (8.5)]"

2) Section 8.5 Geriatric Use in the label will include the opening statement:

"The clinical trials primarily enrolled patients less than 65 years of age. Of the 1022 subjects in clinical studies of DUEXIS, 18% (249 subjects) were 65 years of age or older. Efficacy results in patients who greater than or equal to 65 years of age are summarized in CLINICAL STUDIES section [*see Clinical Studies (14*)]."

3) Section 14 Clinical Studies will include the following information:

> "Subgroup analyses of patients who used low-dose aspirin (less than or equal to 325 mg daily), were 65 years and older, or had a prior history of gastrointestinal ulcer are summarized as follows:
>
> Of the 1022 patients in clinical studies of DUEXIS, 15% (213 patients) used low-dose aspirin and the results were consistent with the overall findings of the study. In these clinical studies 16% of patients who used low-dose aspirin who were treated with DUEXIS developed an upper gastrointestinal ulcer compared to 35% of those patients who received only ibuprofen.
>
> The clinical trials primarily enrolled patients less than 65 years without a prior history of gastrointestinal ulcer. Of the 1022 subjects in clinical studies of DUEXIS, 18% (249 subjects) were 65 years of age or older. In these clinical studies, 23% of patients 65 years of age and older who were treated with DUEXIS developed an upper gastrointestinal ulcer compared to 27% of those patients who received only ibuprofen. [*see Use in Specific Populations (8.5)]*
>
> Of the 1022 subjects in clinical studies of DUEXIS, 6% had a prior history of gastrointestinal ulcer. In these clinical studies, 25% of patients with a prior history of gastrointestinal ulcer who were treated with DUEXIS developed an upper gastrointestinal ulcer compared to 24% of those patients who received only ibuprofen."

Although I remain concerned that this product will not have the efficacy demonstrated in this clinical trial if it is administered to patients with a history of upper gastrointestinal ulcers or in patients who are age 65 years or greater, too few patients with a history of ulcers were studied to draw a definitive conclusion. The number of elderly patients (N 249) seemed reasonable to support concern that the product would not be effective in this subgroup in light of the similar rate of ulcers observed in the Duexis and ibuprofen groups within this subgroup (23% and 27%, respectively). However. the studies that supported the NSAID associated gastric ulcer risk reduction indication in the Nexium label (and described there) enrolled patients who were greater than or equal to age 60 years and/or had a documented history of gastric ulcers. The median age in the trials was 66 years. Patients with a history of obstruction or bleeding from previous gastric ulcer were not excluded from those trials, as they were in the Duexis trials. The treatment effect for Nexium ranged from 7% to 12%. (See Table 6 of this review.) The number of patients in each treatment arm ranged from 184 to 271 in those trials. It is possible that in a sufficiently powered trial the applicant might be able to detect some treatment effect of Duexis in the elderly population.

In summary, I concur with the CDTL and Statistical reviewers' recommendations to approve this NDA. I concur with the recommendations for labeling modification that they made during labeling negotiations with the applicant. Although we have reservations regarding labeling the efficacy analyses based on the applicant's modified intent to treat population, and inclusion of less than conservative outcome analyses, the existence of the SPA that documented FDA agreement with these analyses lead to their inclusion in labeling. Even with conservative analyses, however, the conclusions of the Statistical and Clinical reviewers were that Study 303 efficacy results demonstrated that the product was effective in the population studied, with

a highly persuasive p value. With the FDA preferred conservative analysis, the outcome of Study 301 was not statistically significant, but the crude rates observed in that trial mirrored those observed in 303. In light of the agreement to present the "SPA driven" analysis for Study 301 in the product label, and because the conservative analysis of Study 303 remained highly statistically significant, for the sake of consistency within this product label, the same type of analyses will be presented for each study

8. Safety

This is a 505(b)(2) application. The active ingredients in HZT-501, ibuprofen and famotidine, have been commercially available in the US since 1974 and 1981, respectively. Thus, the individual safety profile of each of these drugs has been well characterized. Additionally, as noted above in the Clinical Pharmacology review, there are no significant interactions between ibuprofen and famotidine resulting in significantly increased exposure for either drug when given together (particularly as predicted for the lower 26.6 mg famotidine dose present in Duexis). The Clinical Pharmacology reviewers found that the ibuprofen component of Duexis is bioequivalent to the referenced approved ibuprofen product, IBU. The total daily dose of the famotidine component of Duexis, with three times daily dosing, is lower than dosing regimens found in the label for the reference product Pepcid.

The CDTL noted in her review that in the safety data base, 1533 patients received at least one dose of study drug in studies 301 or 303; 1022 patients received Duexis and 511 received ibuprofen, 800 mg. Of these 1533 patients, 179 patients continued on treatment) in extension study 304 for a total duration of exposure of 1 year (132 continuing Duexis, and 36 continuing ibuprofen.

There was a single death in the clinical trials, and it occurred in a patient treated in an ibuprofen arm. The death was attributed to acetaminophen toxicity. There were 33 patients (3.2%) with SAEs in the Duexis group and 17 patients (3.3%) in the ibuprofen group. (Note that there was a 2:1 randomization in the phase 3 trials.) The CDTL noted that there were "no substantive imbalances in the types or numbers of SAEs between treatment groups, including cardiovascular SAEs, gastrointestinal SAEs, or infection-related SAEs." The reviewers observed an apparent imbalance in the development of acute renal failure between the combination product and ibuprofen. There were 3 patients in the Duexis treatment group who developed a serious adverse event of acute renal failure. There were no acute renal failure events reported in the ibuprofen comparator group. In this 1533 safety dataset, twice as many patients were treated with Duexis than single agent ibuprofen, due to the 2:1 randomization in the two phase 3 trials. Although all 3 patients with acute renal failure had a history of diabetes mellitus and were taking concomitant medications that could have contributed to development of renal failure (diuretics and/or angiotensin converting enzyme inhibitors and/or angiotensin receptor blockers), the clinical reviewers found that there was a similar distribution of patients with a history of diabetes and hypertension in the safety population between the Duexis and the ibuprofen groups.

In light of the cases of acute renal failure, the Clinical reviewers carefully examined the adverse events (non-SAEs) reported in the safety dataset for other evidence of nephrotoxicity.

They noted that there was a slight imbalance in the overall number of patients who developed any increase (not necessarily to abnormal range) in serum creatinine on study (0.9% or 9 patients for HZT-501 and 0.7% or 2 patients for ibuprofen). Shift tables of patients with normal creatinine at baseline to abnormal creatinine while on study were examined for Study 301 and Study 303. These data, which are summarized in the table below, did not provide conclusive evidence that there is an increased risk of renal impairment in patients who take famotidine in combination with ibuprofen.

Table 9: Shift table of serum creatinine, normal to abnormal*** in controlled studies**

		Study 301		Study 303	
Baseline	Post-Baseline*	DUEXIS N 414 % (n)	Ibuprofen N 207 % (n)	DUEXIS N 598 % (n)	Ibuprofen N 296 % (n)
Normal**	Abnormal***	4% (17)	2% (4)	2 %(15)	4% (12)

*At any point after baseline level
**serum creatinine normal range is 0.5 1.4 mg/dL or 44-124 micromol/L
***serum creatinine >1.4 mg/dL

It is well known that NSAIDs, including ibuprofen, are nephrotoxic, and ibuprofen labeling reflects this. A literature review was conducted to identify reports of nephrotoxicity associated with the specific combination of famotidine with ibuprofen. No reports were identified. The drug interaction (famotidine with ibuprofen) studies submitted for review in this NDA were re-examined by the review team in light of the questions raised by the 3 cases of acute renal failure. As documented in the Clinical Pharmacology review and the Addendum Clinical Pharmacology review, the available drug interaction data do not support that a significant increase in ibuprofen exposure would be anticipated when famotidine is combined with ibuprofen, particularly at the lower famotidine dose found in Duexis. When a higher dose of famotidine, 40 mg, was combined with ibuprofen an approximate 15.6% increase in Cmax of ibuprofen was noted, but there was no impact on the ibuprofen AUC and the reviewers noted the observed change in ibuprofen Cmax was not statistically significant. The Clinical Pharmacology reviewers noted in their addendum review the famotidine 40 mg dose in this drug interaction study would result in a higher famotidine exposure than the predicted steady state famotidine exposure associated with Duexis dosed three times daily.

Based on the information summarized above, I agree with the reviewers' conclusion that the 3 cases of acute renal failure noted in the safety database do not constitute a safety signal, in this dataset where patients treated with Duexis outnumbered those treated with ibuprofen alone, 2:1. The acute renal failure events observed in the trial will be included in the product label, along with the creatinine shift table. Labeling communicates to prescribers that monitoring for the development of nephrotoxicity should be considered. In light of the fact that famotidine is a component of Duexis, and the fact that the Pepcid label states that its dose should be reduced in patients with moderate to severe renal insufficiency (famotidine has a substantial component of renal clearance and famotidine related CNS toxicity has been observed in patients with moderate to severe renal insufficiency due to higher serum levels), the Duexis label will

recommend that patients with moderate to severe renal insufficiency (GFR <50 cc/min) should not take HZT-501 since the famotidine dose cannot be adjusted in this fixed combination.

In an extension study of the phase 3 trials, the proportion of patients who developed SAEs was similar between the Duexis and ibuprofen groups: 8 patients (6.1%) in the Duexis group and 3 patients (6.4%) in the ibuprofen group. The CDTL noted that "there were no substantive imbalances in the types or numbers of SAEs between treatment groups, including cardiovascular SAEs, gastrointestinal SAEs, or infection-related SAEs."

I concur with the reviewers that the safety dataset supports approval of this product. I concur with their recommendations for product labeling.

9. Advisory Committee Meeting

There was no Advisory Committee for this application. The product does not contain a new molecular entity and there were no scientific issues that required discussion in an Advisory Committee.

10. Pediatrics

PREA was triggered for this application because this product includes both a new indication and new dosage form for both ibuprofen and famotidine, and a new dosing regimen for famotidine.

A Pediatric and Maternal Health Staff (PMHS) consult was requested to review a plan to allow (b) (4) Ibuprofen use data were obtained through a consult from the Office of Surveillance and Epidemiology (OSE) Division of Epidemiology to inform the decision. Current ibuprofen pediatric indications include the relief of signs and symptoms of juvenile idiopathic arthritis (JIA), for which chronic use is likely. JIA is extremely uncommon in patients less than 2 years of age. Therefore, studies in children less than two years of age would be highly impractical. The other pediatric indications, fever reduction and relief of mild to moderate pain, are unlikely to be associated with chronic use and the need for a combination product of ibuprofen with famotidine. Based on the consult reviews, the following pediatric studies will be required by the applicant under section 505B(a) of the Federal Food, Drug, And Cosmetic Act. The Pediatric Research Committee (PeRC) found the pediatric studies acceptable.

1758-1 Development of an age appropriate formulation of ibuprofen/famotidine to be used in pediatric patients.

Final Protocol Submission:	July 2013
Study/Trial Completion:	July 2015
Final Report Submission:	March 2016

1758-2 A study to characterize ibuprofen and famotidine pharmacokinetic (PK) parameters following administration of a single dose of a new formulation (suspension) of ibuprofen/famotidine combination in healthy human subjects. PK endpoints must include PK parameters for both ibuprofen and famotidine such as CT, C_{max}, T_{max}, AUC, $T_{1/2}$, clearance, and Vd_{ss}, as applicable.

Final Protocol Submission: July 2016
Study/Trial Completion: December 2016
Final Report Submission: March 2017

1758-3 A study to evaluate the pharmacokinetics (PK) and safety of HZT-501 in children and adolescents ages 10 years through 16 years, 11 months of age who require chronic treatment with NSAIDs. The pediatric study will be a 6-month (24-week), multicenter, open-label study to evaluate the safety of DUEXIS in children and adolescents ages 10 years to 16 years, 11 months.

Final Protocol Submission: October 2011
Study/Trial Completion: October 2013
Final Report Submission: May 2014

1758-4 A study to evaluate the pharmacokinetics (PK) and safety of an age-appropriate formulation of ibuprofen/famotidine to be used in children and adolescents ages 2 years through 9 years, 11 months of age who require chronic treatment with NSAIDs. The pediatric study will be a 6-month (24-week), multicenter, open-label study to evaluate the safety of DUEXIS in children and adolescents ages 2 years to 9 years, 11 months.

Final Protocol Submission: January 2016
Study/Trial Completion: January 2018
Final Report Submission: July 2018

11. Other Relevant Regulatory Issues

Financial Disclosures: The CDTL noted that the applicant reported that of the 894 investigators who participated in the phase 3 trials, financial disclosure information was received for all but 3. Those 3 investigators were removed as investigators from the clinical trials. Signed copies of FDA Form 3454 certifying that the other 891 investigators had not entered into any financial arrangements, whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a) were submitted. None disclosed a proprietary interest in Duexis or significant equity interest in Horizon Therapeutics, Inc. as defined in 21 CFR 54.2(b). No investigator was the recipient of significant payments as defined in 21 CFR 54.2 (f).

DSI: Three clinical sites were chosen for DSI inspection based on the total number of patients enrolled. In addition, one of the three sites appeared to be a higher rate of ulcers in the placebo group relative to other sites. The DSI inspection for a site in Study 303, site 389, detected significant deficiencies that resulted in the investigator being issued a Warning Letter on February 17, 2011. The deficiencies included:

> Failure to ensure that the investigation was conducted according to the investigational plan
>
> Failure to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation

The DSI reviewer concluded that the data generated from this site should not be used in support of the NDA.

In light of the DSI findings at Site 389, the clinical reviewers requested two additional DSI inspections in Study 303 to address questions regarding the adequacy of the applicant's study monitoring procedures. The reviewers determined that this additional information was needed to assure them of the validity of the results from Study 303. The two additional study sites for Study 303 were selected because there were relatively large numbers of patients who terminated the study early at the sites. In addition, an inspection of Horizon Pharma, Inc. was requested to ensure that the applicant had provided proper oversight of the clinical trials.

Late in the review cycle, results of the DSI inspection at one of the additional two sites (site 363) identified deficiencies that called the validity of the data in four patients into question (patients 005, 021, 050, and 100). In this case, the DSI reviewer recommended that these four patients should also be excluded from all efficacy analyses. The inspection at Horizon Pharma, Inc. did not uncover any substantive deficiencies. The DSI reviewer concluded that study 303 data (with the exception of 4 patients from site 363, and 167 patients from site 389) were valid and could be reviewed. Efficacy analyses were performed excluding these patients, and their removal did not impact the observed outcome.

Additionally, as discussed in the Clinical Pharmacology section of this review, a DSI inspection was requested for the clinical and analytical portions of one of the bioequivalence studies submitted to support this 505(b)(2) application. The reviewers required this inspection because the clinical formulation and the to-be-marketed formulation were different. Ultimately, all issues identified in that inspection were considered to have been adequately addressed, and the DSI reviewers concluded that the data from the study could be used to support the application (with the exception of elimination of a patient from the analyses). After reading their final reviews, I received clarifying confirmation from them via email that the study data could be used to support the application and that no post marketing commitments were necessary based on their inspection findings.

Combination Rule: The proposed product is a fixed combination drug product. The applicant has established that each component contributes to the purported treatment effect of the product, meeting the requirements of the combination rule.

Medication Guide: Because the ibuprofen component of Duexis is an NSAID, this combination product is subject to the class labeling for NSAID products, including a Box Warning and Medication Guide. The Medication Guide was "updated" to be relevant for Duexis, i.e., to also provide patients information on the famotidine component of the product.

12. Labeling

I concur with the reviewers' recommendations for labeling. The DMEPA reviewers rejected the proposed proprietary name, (b) (4) A new proposed name, Duexis, was submitted for review and was found acceptable by the DMEPA reviewers.

The proposed labeling that the applicant submitted in the NDA (b) (4) The applicant agreed to revise the label (b) (4)

The label will include the class labeling Box Warning and Medication Guide for the NSAID (ibuprofen) component of Duexis.

See additional information on labeling included in other sections of this review.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action Approval.

- Risk Benefit Assessment I concur with the CDTL that the risk and benefit characteristics of this fixed combination product are favorable, for the proposed indication. Both product components have been marketed for years. The indications for ibuprofen that will appear in the Duexis product label are currently found in the ibuprofen reference product, to which Duexis is bioequivalent. The reduction of risk of upper gastrointestinal ulcers secondary to ibuprofen indication is a new indication for famotidine, and the famotidine dose and dosing regimen (three times daily as part of this combination product) is also new. The applicant has established that the product is safe and effective for this indication.

Because the phase 3 trials submitted in support of this application to establish the effectiveness of the famotidine component of Duexis for reduction of upper gastrointestinal ulcers related to ibuprofen enrolled few patients with a history of upper gastrointestinal ulcers, and because the 18% of patients in the clinical trials (N 249) who were ≥ 65 years of age did not appear to have a treatment effect comparable to the rest of the study population, the indication will include a statement describing the limitation of the actual population studied in these trials ("The clinical trials primarily enrolled patients less than 65 years of age without a prior history of gastrointestinal ulcer."). Prescribers should not assume that the product will have the same efficacy in higher risk population of patients ≥ 65 years of age or patients who have a history of upper gastrointestinal ulcers.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

  Because this fixed combination product contains the NSAID ibuprofen, it will be approved with the Medication Guide that all NSAID products carry in labeling. (See Approval Letter and Section 11 above.)

- Recommendation for other Postmarketing Requirements and Commitments

See Section 10 of this review and/or the NDA approval letter for the list of pediatric postmarketing studies that will be required under Section 505B(a) of the Federal Food, Drug, and Cosmetic Act.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DONNA J GRIEBEL
04/23/2011